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(54) Title: METHOD OF TREATING HAIR LOSS USING NON-IMMUNOSUPPRESSIVE COMPOUNDS		
(57) Abstract The present disclosure describes methods for treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth. The methods comprise administering a non-immunosuppressive compound having a structure as described herein and a pharmaceutically-acceptable carrier.		

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METHOD OF TREATING HAIR LOSS USING NON-IMMUNOSUPPRESSIVE COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to methods for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth.

BACKGROUND OF THE INVENTION

Hair loss is a common problem which occurs, for example, through natural processes or is often chemically promoted through the use of certain therapeutic drugs designed to alleviate conditions such as cancer. Often such hair loss is accompanied by lack of hair regrowth which causes partial or full baldness.

As is well-known in the art, hair growth occurs by a cycle of activity which involves alternating periods of growth and rest. This cycle is often divided into three main stages which are known as anagen, catagen, and telogen. Anagen is the growth phase of the cycle and may be characterized by penetration of the hair follicle deep into the dermis with rapid proliferation of cells which are differentiating to form hair. The next phase is catagen, which is a transitional stage marked by the cessation of cell division, and during which the hair follicle regresses through the dermis and hair growth is ceased. The next phase, telogen, is often characterized as the resting stage during which the regressed follicle contains a germ with tightly packed dermal papilla cells. At telogen, the initiation of a new anagen phase is caused by rapid cell proliferation in the germ, expansion of the dermal papilla, and elaboration of basement membrane components. Wherein hair growth ceases, most of the hair follicles reside in telogen and anagen is not engaged, thus causing the onset of full or partial baldness.

There have been many attempts in the literature to invoke the regrowth of hair by, for example, the promotion or prolongation of anagen. Currently, there are two drugs approved by the United States Food and Drug Administration for the treatment of male pattern baldness: topical minoxidil (marketed as Rogaine® by Pharmacia & Upjohn), and oral finasteride (marketed as Propecia® by Merck & Co., Inc.). For several reasons, however, including safety concerns and / or lack of efficacy, the search for efficacious hair growth inducers is ongoing.

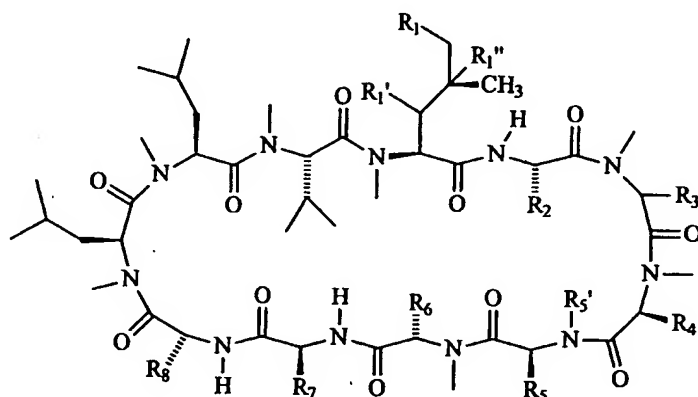
Interestingly, cyclosporin A is known to invoke a prominent hair induction side effect. Unfortunately, however, cyclosporin A is not practical for use as a hair growth agent due to its strongly immunosuppressive activity. See Yamamoto et al., "Hair Growth-Stimulating Effects of Cyclosporin A and FK506, Potent Immunosuppressants", *Journal of Dermatological Science*, Vol. 7 (suppl.), pp. S47 - S54 (1994); Maurer et al., "Hair Growth Modulation by Topical Immunophilin Ligands", *American Journal of Pathology*, Vol. 150, No. 4, pp. 1433 - 1441 (1997); Paus et al., "Hair Growth Control by Immunosuppression", *Archives of Dermatological Research*, Vol. 288, pp. 408 - 410 (1996); Paus et al., "Cyclosporin A, PSC 833 and FK 506, but not Cyclosporin H and Rapamycin, Induce Anagen and Inhibit Catagen in Murine Skin", *The Journal of Investigative Dermatology*, Vol. 101, p. 420 (1994); Paus et al., "Cyclosporin A, FK506 and Related Drugs as Tools for Hair Research", *Archives of Dermatological Research*, Vol. 285, p. 80 (1993); and Traber et al., "Cyclosporins - New Analogues by Precursor Directed Biosynthesis", *The Journal of Antibiotics*, Vol. 42, No. 4, pp. 591 - 597 (1988).

It has been reported that PSC833, which is a non-immunosuppressive analog of cyclosporin D, induces anagen in mice at a weaker level than cyclosporin A. See Paus et al., "Cyclosporin A, PSC 833 and FK 506, but not Cyclosporin H and Rapamycin, Induce Anagen and Inhibit Catagen in Murine Skin", *The Journal of Investigative Dermatology*, Vol. 101, p. 420 (1994); Paus et al., "Cyclosporin A, FK506 and Related Drugs as Tools for Hair Research", *Archives of Dermatological Research*, Vol. 285, p. 80 (1993).

Based on the weaker effect of PSC833 as compared to cyclosporin A, the challenge has been to provide non-immunosuppressive analogs of cyclosporin A which exhibit hair growth induction approaching that of cyclosporin A itself. Surprisingly, the present inventors have discovered analogs of cyclosporin A which are devoid of immunosuppressive activity yet induce hair growth at levels comparable to cyclosporin A. Accordingly, potent methods of treating hair loss using cyclosporin A analogs which are practical for use are provided herein.

SUMMARY OF THE INVENTION

The present invention relates to methods for treating hair loss comprising administering to a mammal a non-immunosuppressive compound which has been found by the present inventors to be particularly useful for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth. The compounds utilized in the present method have the structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein R_1 , R_1' , R_1'' , R_2 , R_3 , R_4 , R_5 , R_5' , R_6 , R_7 , and R_8 are as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of using compounds and compositions which are particularly useful for treating hair loss in mammals, preferably humans, including arresting and / or reversing hair loss and promoting hair growth.

In addition to discovering that the present compounds are useful for treating hair loss, the present inventors have also surprisingly discovered that immunosuppression is not required for hair growth stimulation. The present inventors have further discovered compounds that are useful for treating hair loss but are surprisingly non-immunosuppressive. The compounds useful in the method of the present invention are therefore, as defined herein, non-immunosuppressive.

Publications and patents are referred to throughout this disclosure. All references cited herein are hereby incorporated by reference.

All percentages, ratios, and proportions used herein are by weight unless otherwise specified.

Definition and Usage of Terms

The following is a list of definitions for terms used herein:

As used herein "salt" is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art. Preferred cationic salts include the alkali metal salts (such as, for example, sodium and potassium), alkaline earth metal salts (such as, for example, magnesium and calcium), and organic salts. Preferred anionic salts include the halides (such as, for example, chloride salts). Such acceptable salts must, when administered, be appropriate for mammalian use.

As used herein, "alkenyl" is an unsaturated hydrocarbon chain radical. Alkenyls have at least one double bond. Unless otherwise specified, alkenyls have from 2 to about 15 carbon atoms ($C_2 - C_{15}$); preferably from 2 to about 10 carbon atoms ($C_2 - C_{10}$); more preferably from 2 to about 8 carbon atoms ($C_2 - C_8$), and most preferably from 2 to about 6 carbon atoms ($C_2 - C_6$). Non-limiting examples of alkenyls include vinyl, allyl, and butenyl.

As used herein, "alkoxy" is an oxygen radical having an alkyl, alkenyl, or alkynyl, preferably an alkyl or alkenyl, and most preferably an alkyl substituent. Examples of alkoxy radicals include -O-methyl and -O-ethyl.

As used herein, "alkyl" is a saturated hydrocarbon chain radical. Unless otherwise specified, alkyls have from 1 to about 15 carbon atoms ($C_1 - C_{15}$); preferably from 1 to about 10 carbon atoms ($C_1 - C_{10}$); more preferably from 1 to about 6 carbon atoms ($C_1 - C_6$); and most preferably from 1 to about 4 carbon atoms ($C_1 - C_4$). Preferred alkyls include, for example, methyl, ethyl, propyl, *iso*-propyl, and butyl.

As used herein, "alkynyl" is an unsaturated hydrocarbon chain radical. Alkynyls have at least one triple bond. Unless otherwise specified, alkynyls have from 2 to about 15 carbon atoms ($C_2 - C_{15}$); preferably from 2 to about 10 carbon atoms ($C_2 - C_{10}$); more preferably from 2 to about 8 carbon atoms ($C_2 - C_8$), and most preferably from 2 to about 6 carbon atoms ($C_2 - C_6$).

As used herein, "biohydrolyzable amides" are amides of the compounds used in the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable esters" are esters of the compounds used in the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable imides" are imides of the compounds used in the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, a "lower" moiety (e.g., "lower" alkyl) is a moiety having 1 to about 6, preferably 1 to about 4, carbon atoms.

As used herein, "pharmaceutically acceptable" means suitable for use in a human or other mammal.

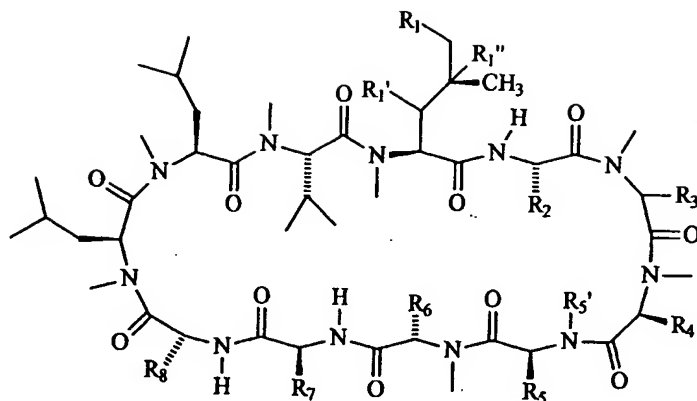
As used herein, "safe and effective amount of a compound" (or composition, or the like) means an amount that is effective to exhibit biological activity, preferably wherein the biological activity is arresting and / or reversing hair loss or promoting hair growth, at the site(s) of activity in a mammalian subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit / risk ratio when used in the manner of this invention.

As used herein, substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979). As used herein unless otherwise specified, the term "substituted" in reference to a group, moiety, or the like, preferably means having one or more substituent groups each independently selected from hydrogen, alkyl, alkenyl, alkoxy, hydroxy, oxo, nitro, amino, alkylamino, cyano, halo, carboxy, alkoxyacyl (e.g., carboethoxy), thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (e.g., piperidinyl, morpholinyl, pyrrolidinyl), imino, thioxo, hydroxyalkyl, aryloxy, and arylalkyl, more preferably hydrogen, alkyl, alkenyl, alkoxy, hydroxy, oxo, nitro, amino, alkylamino, halo, thiol, and aryloxy, even more preferably hydrogen, alkyl, alkenyl, alkoxy, hydroxy, nitro, amino, alkylamino, and halo, still more preferably hydrogen, alkyl, and alkoxy, and most preferably alkoxy.

As used herein, wherein any variable, moiety, group, or the like occurs more than one time in any variable or structure, its definition at each occurrence is independent of its definition at every other occurrence.

Methods of the Present Invention

The present invention relates to methods of treating hair loss comprising administering to a mammal a composition comprising a compound having the structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein:

- (a) R_1 is selected from the group consisting of 1-propenyl, propyl, 3-hydroxy-1-propenyl, -O-methyl, -O-*p*-benzoyl benzyl, and hydroxy;
- (b) R_1' is selected from hydroxy, oxo, and acyloxy;
- (c) R_1'' is selected from hydrogen and methyl;
- (d) R_2 is selected from ethyl, *n*-butyl, 2-hydroxypropyl, 2-methoxypropyl, 1-methylpropyl, and 2-acyloxy-propyl;
- (e) R_3 is selected from hydrogen, methyl, benzyl, 1-propenyl, and 2-methyl-3-hydroxy-propyl;
- (f) R_4 is substituted or unsubstituted $C_1 - C_3$ straight or branched alkyl;
- (g) R_5 is substituted or unsubstituted $C_1 - C_6$ straight or branched alkyl;
- (h) R_5' is selected from hydrogen, methyl, benzyl, *p*-fluorobenzyl, 1-propenyl, and 1-phenyl-1-propenyl;
- (i) R_6 is selected from 2-methylpropyl, 2-methyl-3-hydroxypropyl, methyl, and ethyl;
- (j) R_7 is selected from methyl and phenyl; and
- (k) R_8 is selected from methyl and hydroxymethyl.

The R_1 Moiety

The R_1 moiety is selected from 1-propenyl, propyl, 3-hydroxy-1-propenyl, -O-methyl, -O-*p*-benzoyl benzyl, and hydroxy. More preferably, R_1 is selected from 1-propenyl, propyl, and 3-hydroxy-1-propenyl, most preferably R_1 is 1-propenyl.

The R_1' Moiety

The R_1' moiety is selected from hydroxy, oxo, and acyloxy. As used herein, the term "oxo" means a doubly bonded oxygen radical. As used herein, the term "acyloxy" is an oxygen radical having an acyl substituent. "Acyl" means a radical which could be formed by removal of the hydroxy from a carboxylic acid (i.e., $X-C(=O)-$), wherein X is any substituent but preferably selected from alkyl, alkenyl, alkynyl, and aryl, most preferably alkyl. Thus, for example, "acyloxy" is illustrated by $-O-C(=O)-alkyl$.

While both hydroxy and oxo are both highly preferred, the most preferred R_1' moiety is oxo.

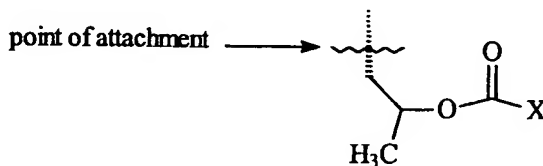
The R_1'' Moiety

The R_1'' moiety is selected from hydrogen and methyl. Most preferably, R_1'' is hydrogen.

These R_1 , R_1' , and R_1'' moieties are further described in, for example, U.S. Patent No. 5,767,069, Ko et al., assigned to Novartis, issued June 16, 1998; WO 97/18828, Steiner et al., assigned to Guilford Pharmaceuticals, Inc., published May 29, 1997; and Bartz et al., "Inhibition of Human Immunodeficiency Virus Replication by Nonimmunosuppressive Analogs of Cyclosporin A", *Proceedings of the National Academy of Sciences U.S.A.*, Vol. 92, pp. 5381 - 5385 (1995).

The R_2 Moiety

The R_2 moiety is selected from ethyl, *n*-butyl, 2-hydroxypropyl, 2-methoxypropyl, 1-methylpropyl, and 2-acyloxy-propyl. As used herein, the term "acyloxy" is an oxygen radical having an acyl substituent. "Acyl" means a radical which could be formed by removal of the hydroxy from a carboxylic acid (i.e., $X-C(=O)-$), wherein X is preferably selected from alkyl, alkenyl, alkynyl, and aryl. Thus, 2-acyloxy-propyl is exemplified by:



wherein X is any substituent but preferably selected from alkyl, alkenyl, alkynyl, and aryl, most preferably alkyl.

R_2 is preferably selected from ethyl, *n*-butyl, 2-hydroxypropyl, and 2-methoxypropyl. Most preferably, R_2 is ethyl.

These R₂ moieties are further described in, for example, U.S. Patent No. 5,767,069, Ko et al., assigned to Novartis, issued June 16, 1998; and WO 97/18828, Steiner et al., assigned to Guilford Pharmaceuticals, Inc., published May 29, 1997.

The R₃ Moiety

The R₃ moiety is selected from hydrogen, methyl, benzyl, 1-propenyl, and 2-methyl-3-hydroxy-propyl. Preferably, R₃ is selected from hydrogen, methyl and benzyl. Most preferably R₃ is hydrogen or benzyl.

These R₃ moieties are further described in, for example, U.S. Patent No. 5,767,069, Ko et al., assigned to Novartis, issued June 16, 1998; WO 97/18828, Steiner et al., assigned to Guilford Pharmaceuticals, Inc., published May 29, 1997; and Hu et al., "Cyclosporin Analogs Modified in the 3,7,8-Positions: Substituent Effects on Peptidylprolyl Isomerase Inhibition and Immunosuppressive Activity Are Nonadditive", *Journal of Medicinal Chemistry*, Vol. 38, pp. 4164 - 4170 (1995).

With respect to stereochemistry at the R₃ position, the R₃ moiety may be in the L or D configuration, but is preferably in the D configuration.

The R₄ Moiety

The R₄ moiety is substituted or unsubstituted C₁ - C₉ straight or branched alkyl, preferably substituted or unsubstituted C₁ - C₆ straight or branched alkyl, and more preferably substituted or unsubstituted C₁ - C₄ straight or branched alkyl.

Preferably, R₄ is selected from 2-methylpropyl, 2-methyl-3-hydroxypropyl, 2-methylbutyl, *iso*-propyl, 2-hydroxypropyl, and methyl. Most preferably, R₄ is 2-methylpropyl.

These R₄ moieties are further described in, for example, U.S. Patent No. 5,767,069, Ko et al., assigned to Novartis, issued June 16, 1998; WO 97/18828, Steiner et al., assigned to Guilford Pharmaceuticals, Inc., published May 29, 1997; and Bartz et al., "Inhibition of Human Immunodeficiency Virus Replication by Nonimmunosuppressive Analogs of Cyclosporin A", *Proceedings of the National Academy of Sciences U.S.A.*, Vol. 92, pp. 5381 - 5385 (1995).

The R₅ Moiety

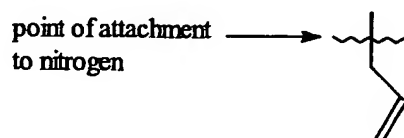
The R₅ moiety is substituted or unsubstituted C₁ - C₆ straight or branched alkyl, and more preferably substituted or unsubstituted C₁ - C₄ straight or branched alkyl.

Preferably R₅ is selected from 2-methylpropyl, *n*-butyl and *iso*-propyl. Most preferably, R₅ is *iso*-propyl.

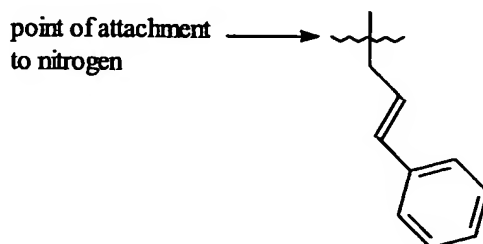
These R_5 moieties are further described in, for example, U.S. Patent No. 5,767,069, Ko et al., assigned to Novartis, issued June 16, 1998; and WO 97/18828, Steiner et al., assigned to Guilford Pharmaceuticals, Inc., published May 29, 1997.

The R_5' Moiety

The R_5' moiety is selected from hydrogen, methyl, benzyl, *p*-fluorobenzyl, 1-propenyl, and 1-phenyl-1-propenyl. For clarity, 1-propenyl is exemplified as:



For further clarity, 1-phenyl-1-propenyl is exemplified as:



See also, Papageorgiou et al., "Conformational Control of Cyclosporin Through Substitution of the N-5 Position. A New Class of Cyclosporin Antagonists", *Bioorganic & Medicinal Chemistry*, Vol. 5, No. 1, pp. 187 - 192 (1997).

Preferably, R_5' is selected from hydrogen, methyl, and 1-propenyl, more preferably hydrogen and 1-propenyl. Most preferably, R_5' is hydrogen.

The R_6 Moiety

The R_6 moiety is selected from 2-methylpropyl, 2-methyl-3-hydroxypropyl, methyl, and ethyl, more preferably, 2-methylpropyl and 2-methyl-3-hydroxypropyl. Most preferably, R_6 is 2-methylpropyl.

These R_6 moieties are further described in, for example, U.S. Patent No. 5,767,069, Ko et al., assigned to Novartis, issued June 16, 1998; and WO 97/18828, Steiner et al., assigned to Guilford Pharmaceuticals, Inc., published May 29, 1997.

The R₇ Moiety

The R₇ moiety is selected from methyl and phenyl. Preferably, R₇ is methyl.

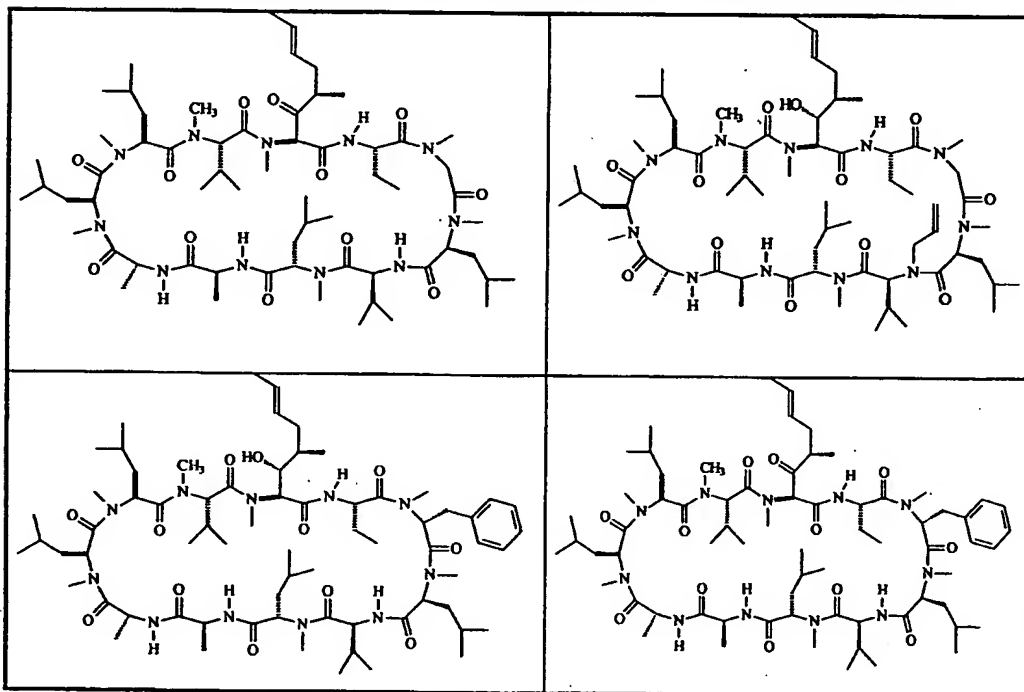
These R₇ moieties are further described in, for example, WO 97/18828, Steiner et al., assigned to Guilford Pharmaceuticals, Inc., published May 29, 1997 and Hu et al., "Cyclosporin Analogs Modified in the 3,7,8-Positions: Substituent Effects on Peptidylprolyl Isomerase Inhibition and Immunosuppressive Activity Are Nonadditive", *Journal of Medicinal Chemistry*, Vol. 38, pp. 4164 - 4170 (1995).

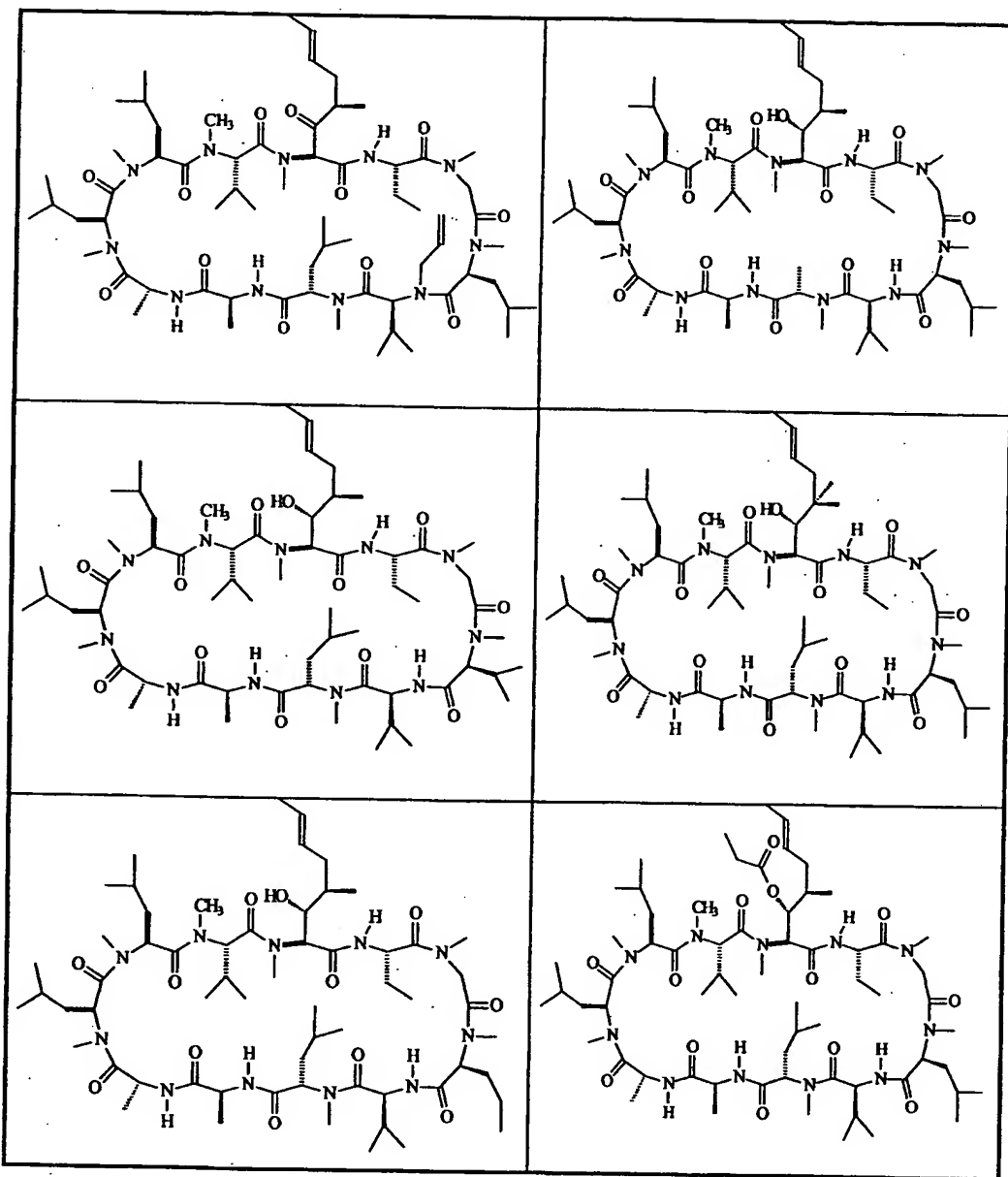
The R₈ Moiety

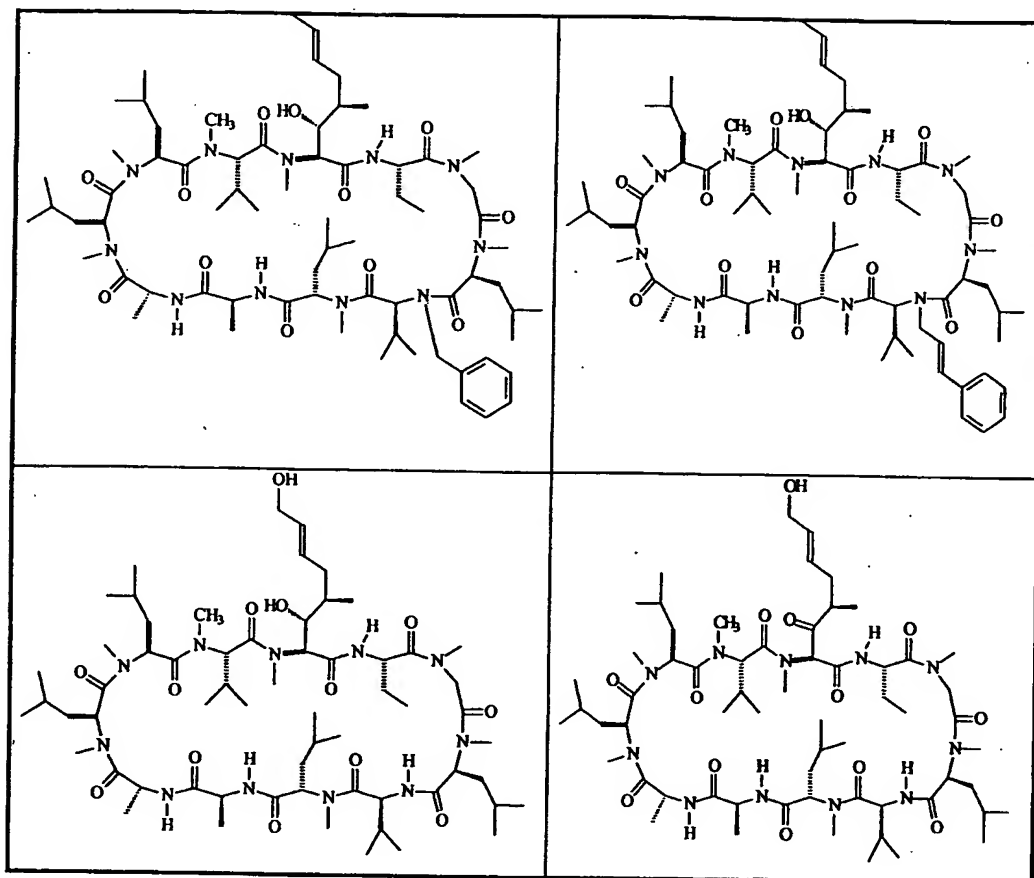
The R₈ moiety is selected from methyl and hydroxymethyl. Preferably, R₈ is methyl.

These R₈ moieties are further described in, for example, WO 97/18828, Steiner et al., assigned to Guilford Pharmaceuticals, Inc., published May 29, 1997 and Hu et al., "Cyclosporin Analogs Modified in the 3,7,8-Positions: Substituent Effects on Peptidylprolyl Isomerase Inhibition and Immunosuppressive Activity Are Nonadditive", *Journal of Medicinal Chemistry*, Vol. 38, pp. 4164 - 4170 (1995).

Preferred compounds useful in the methods of the present invention are shown below:







Analytical Methods

The present invention relates to methods of treating hair loss in mammals by administering to a mammal a non-immunosuppressive compound having a structure as described herein. Compounds (test compounds) may be tested for their ability to induce anagen and their immunosuppressive activity (or lack thereof) using the following methods. Alternatively, other methods well-known in the art may be used (but with the term "non-immunosuppressive" being defined according to the method disclosed herein below).

Telogen Conversion Assay:

The Telogen Conversion Assay measures the potential of a test compound to convert mice in the resting stage of the hair growth cycle ("telogen"), to the growth stage of the hair growth cycle ("anagen").

Without intending to be limited by theory, there are three principal phases of the hair growth cycle: anagen, catagen, and telogen. It is believed that there is a longer telogen period in

C3H mice (Harlan Sprague Dawley, Inc., Indianapolis, IN) from approximately 40 days of age until about 75 days of age, when hair growth is synchronized. It is believed that after 75 days of age, hair growth is no longer synchronized. Wherein about 40 day-old mice with dark fur (brown or black) are used in hair growth experiments, melanogenesis occurs along with hair (fur) growth wherein the topical application of hair growth inducers are evaluated. The Telogen Conversion Assay herein below is used to screen compounds for potential hair growth by measuring melanogenesis.

Three groups of 44 day-old C3H mice are utilized: a vehicle control group, a positive control group, and a test compound group, wherein the test compound group is administered a compound used in the method of the present invention. The length of the assay is at least 19 days with 15 treatment days (wherein the treatment days occur Mondays through Fridays). Day 1 is the first day of treatment. Most studies will end on Day 19, but a few may be carried out to Day 24 if the melanogenesis response looks positive, but occurs slowly. A typical study design is shown in Table 1 below:

Table 1

Group #	Animal #	Compound	Concentration	Application volume	Length of Study
1	1 - 10	Test Compound	5% in vehicle**	400 μ L topical	19 or 24 days
2	11 - 20	Cyclosporin A	0.19% in vehicle**	400 μ L topical	19 or 24 days
3	21 - 30	Vehicle**	N/A	400 μ L topical	19 or 24 days

**The vehicle is 60% ethanol, 20% propylene glycol, and 20% dimethyl isosorbide (commercially available from Sigma Chemical Co., St. Louis, MO).

The mice are treated topically Monday through Friday on their lower back (base of tail to the lower rib). A pipettor and tip are used to deliver 400 μ L to each mouse's back. The 400 μ L application is applied slowly while moving hair on the mouse to allow the application to reach the skin.

While each treatment is being applied to the mouse topically, a visual grade of from 0 to 4 will be given to the skin color in the application area of each animal. As a mouse converts from telogen to anagen, its skin color will become more bluish-black. As indicated in Table 2, the grades 0 to 4 represent the following visual observations as the skin progresses from white to bluish-black.

Table 2

<u>Visual Observation</u>	<u>Grade</u>
Whitish Skin Color	0
Skin is light gray (indication of initiation of anagen)	1
Appearance of Blue Spots	2
Blue Spots are aggregating to form one large blue area	3
Skin is dark blue (almost black) with color covering majority of treatment area (indication of mouse in full anagen)	4

Immunosuppression Assay:

The immunosuppression assay herein predicts the immunosuppressive activity (or non-immunosuppressive activity) of a compound used in the method of the present invention. The assay is performed as follows:

Spleens are excised from euthanized (CO₂ asphyxiation) adult male C3H mice ranging in age from seven to sixteen weeks old (live mice commercially available from Harlan Sprague Dawley, Inc., Indianapolis, IN). The spleens are placed immediately in cold Hanks Balanced Salt Solution (HBSS, commercially available from Gibco-BRL, Gaithersburg, MD). The spleens are then ground up between frosted glass slides and filtered through a sterile screen to remove tissue debris. The resulting cell suspension is underlayered with an equal volume of Ficoll-Paque Plus (commercially available from Pharmacia Biotech, Piscataway, NJ) and centrifuged at 400 x g for approximately forty minutes at 20 °C in order to collect the splenocytes. The splenocytes are collected from the interface using a disposable pipet and are washed twice with HBSS, followed by centrifugation at 100 x g for ten minutes at 20 °C. Splenocytes are resuspended in five to ten mL of cell culture media consisting of phenol red-free RPMI 1640 (culture media commercially available from Gibco-BRL) containing 10% heat-inactivated fetal bovine serum (Gibco-BRL), penicillin (50 U/mL), streptomycin (100 µg/mL), L-glutamine (2 mM), 2-mercaptoethanol (10⁻⁵ M), and N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (10 mM). The cells are counted and checked for viability using, for example, trypan blue. Splenocytes are resuspended in medium at 10⁶ cells/mL and pipetted into 96 well round bottom plates at 10⁵ cells/well. Splenocytes are activated by addition of 50 µL/well of concanavalin A (final assay concentration = 5 µg/ml) in the presence or absence of a test compound. Test compounds are made up as stock solutions in methyl sulfoxide (DMSO), then diluted in medium and 50 µL/well added, such that the final concentration of DMSO in the assay is below 0.05%. The plates are incubated at 37 °C

with 5% CO₂ for 48 hours. After 48 hours, the cells are pulsed with 1 μ Ci/well of methyl-³H-thymidine (commercially available from Amersham, Buckinghamshire, England) and incubated an additional 24 hours.

After 24 hours, the cells are harvested onto GF/C filter plates (commercially available from Packard, Downers Grove, IL), solubilized in Microscint 20 (Packard), and counted on a TopCount microplate scintillation and luminescence plate counter (Packard). Activity is measured as a percentage of control activity in the absence of test compound and plotted *versus* test compound concentration. The data are fit to a 4-parameter curve fit (Sigmaplot) and IC₅₀ values are calculated. As used herein, test compounds are considered non-immunosuppressive if, by using this method, the ratio of (cyclosporin A IC₅₀/test compound IC₅₀) x 100 is less than or equal to 0.02, *i.e.*, as defined herein, a non-immunosuppressive test compound has \leq 2% of the immunosuppressive activity of cyclosporin A.

Cell viability is assessed using the MTT (3-[4,5-dimethyl-thiazoyl-2-yl]2,5-diphenyl-tetrazolium bromide) dye assay as described by Nelson et al., *Journal of Immunology*, Vol. 150, No. 6, pp. 2139 - 2147 (1993), with the exception that the assay is carried out in serum-free, phenol red-free RPMI 1640 and the dye is solubilized in 100 μ L/well DMSO and read at an OD of 540 nm with a background correction at 650 nm on a SpectraMax Plus microplate reader (Molecular Devices, Menlo Park, CA).

Method of Making

The compounds used in the methods of the present invention are prepared according to procedures which are well-known to those skilled in the art. The starting materials used in preparing the compounds are known, made by known methods, or are commercially available as a starting material.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out standard manipulations of organic compounds without further direction. Examples of such manipulations are discussed in standard texts such as J. March, Advanced Organic Chemistry, John Wiley & Sons (1992).

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionalities are masked or protected in the compound, thus increasing the yield of the reaction and / or avoiding any undesirable side reactions. Often, the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan.

Examples of many such manipulations can be found in, for example, T. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons (1981).

The compounds of the present invention may have one or more chiral centers. As a result, one may selectively prepare one optical isomer, including diastereomers and enantiomers, over another, for example by chiral starting materials, catalysts or solvents, or may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures, mixtures of optical isomers, including diastereomers and enantiomers, may be separated using known methods, such as through the use of, for example, chiral salts and chiral chromatography.

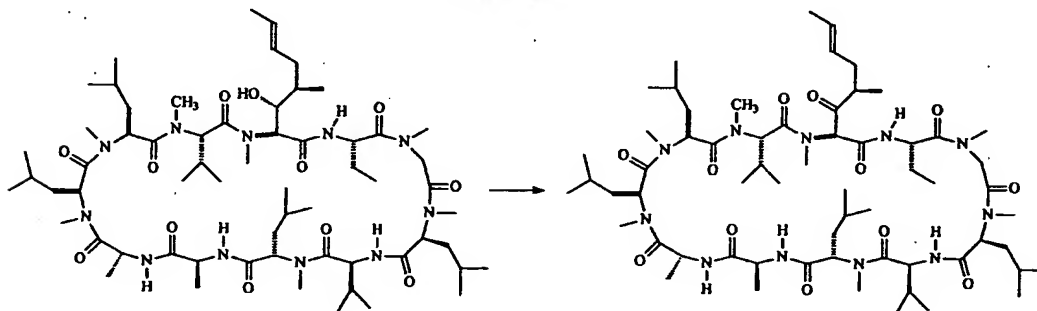
In addition, it is recognized that one optical isomer, including a diastereomer and enantiomer, or a stereoisomer, may have favorable properties over the other. Thus, when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

The syntheses of the compounds useful in the present invention are described in the art. Accordingly, the ordinarily skilled artisan will be able to prepare the compounds described herein. For further guidance, the following references describe syntheses of the compounds utilized in the present method: Bartz et al., "Inhibition of Human Immunodeficiency Virus Replication by Nonimmunosuppressive Analogs of Cyclosporin A", *Proceedings of the National Academy of Sciences U.S.A.*, Vol. 92, pp. 5381 - 5385 (1995); WO 98/28328, Barriere et al., assigned to Rhone-Poulenc, published July 2, 1998; U.S. Patent No. 5,643,870, Boelsterli et al., assigned to Sandoz Ltd., issued July 1, 1997; U.S. Patent No. 5,525,590, Bollinger et al., assigned to Sandoz Ltd., issued June 11, 1996; U.S. Patent No. 5,116,816, Dreyfuss et al., assigned to Sandoz Ltd., issued May 26, 1992; U.S. Patent No. 5,284,826, Eberle, assigned to Sandoz Ltd., issued February 8, 1994; U.S. Patent No. 5,807,820, Elias, assigned to Novartis, issued September 15, 1998; Hu et al., "Cyclosporin Analogs Modified in the 3,7,8-Positions: Substituent Effects on Peptidylprolyl Isomerase Inhibition and Immunosuppressive Activity Are Nonadditive", *Journal of Medicinal Chemistry*, Vol. 38, pp. 4164 - 4170 (1995); U.S. Patent No. 5,767,069, Ko et al., assigned to Novartis, issued June 16, 1998; Papageorgiou et al., "Conformational Control of Cyclosporin through Substitution of the N-5 Position. A New Class of Cyclosporin Antagonists", *Bioorganic & Medicinal Chemistry*, Vol. 5, pp. 187 - 192 (1997); Rich et al., "Synthesis, Biological Activity, and Conformational Analysis of (2S, 3R, 4S)-MeBmt¹-cyclosporin, a Novel 1-Position Epimer of Cyclosporin A", *Journal of Medicinal Chemistry*, Vol. 32, pp. 1982 - 1987 (1989); EP 0,194,972, Seebach, assigned to Sandoz Ltd.,

published September 17, 1986; U.S. Patent No. 4,703,033, Seebach, assigned to Sandoz Ltd., issued October 27, 1987; U.S. Patent No. 4,771,122, Seebach, assigned to Sandoz Ltd., issued September 13, 1988; WO 97/18828, Steiner et al., assigned to Guilford Pharmaceuticals, Inc., published May 29, 1997; Sun et al., "Synthesis, Conformation, and Immunosuppressive Activity of Cyclosporins That Contain ϵ -Oxygen (4R)-4-[(E)-Butenyl]-4,N-dimethyl-L-threonine Analogs in the 1-Position", *Journal of Medicinal Chemistry*, Vol. 33, pp. 1443 - 1452 (1990); U.S. Patent No. 4,289,851, Traber et al., assigned to Sandoz Ltd., issued September 15, 1981; Traber et al., "Cyclosporins - New Analogues by Precursor Directed Biosynthesis", *The Journal of Antibiotics*, Vol. 42, No. 4, pp. 591 - 597 (1988); U.S. Patent No. 4,764,503, Wenger, assigned to Sandoz Ltd., issued August 16, 1988; and WO 93/17039, Wenger, assigned to Sandoz Ltd., published September 2, 1993.

As even further guidance, the following non-limiting examples illustrate methods of making preferred compounds used in the present invention:

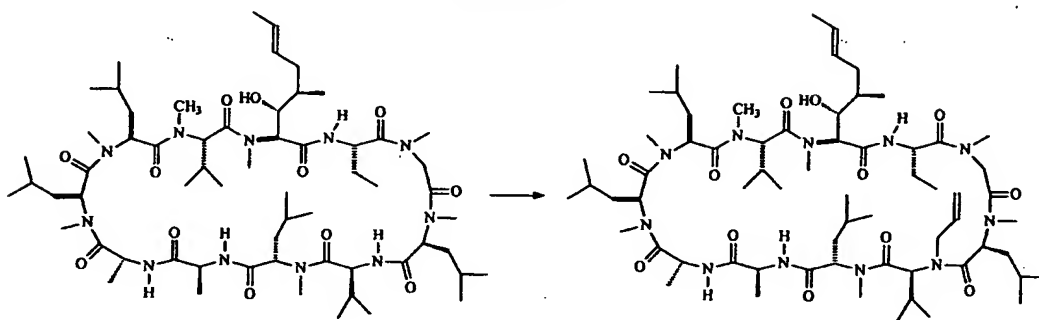
Example 1



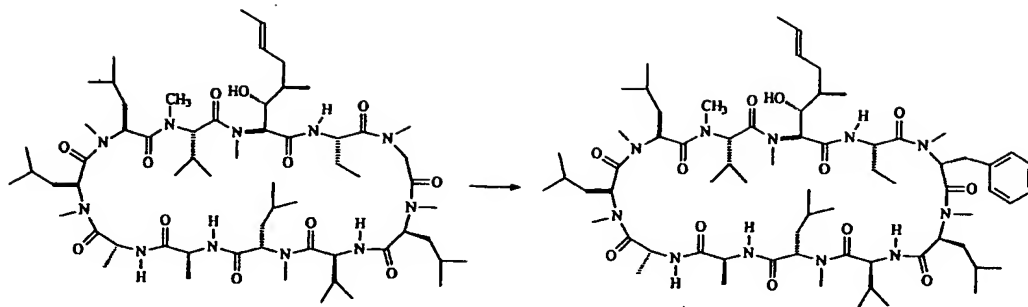
(3'-keto)cyclosporin A: Dess-Martin periodinane (2.12 g, 5 mmol; prepared according to the procedure reported in Ireland et al., "An Improved Procedure for the Preparation of the Dess-Martin Periodinane", *Journal of Organic Chemistry*, Vol. 58, p. 2899 (1993)) is combined with dichloromethane (20 mL) and stirred for 10 minutes at ambient temperature. The solution is chilled to 5 °C and a solution of cyclosporin A (2 g, 1.66 mmol; commercially available from Alexis Corporation, San Diego, CA) in dichloromethane (40 mL) is added dropwise over 10 minutes. The mixture is stirred at 5 °C for 1 hour followed by addition of a solution of sodium thiosulfate (5.53 g, 35 mmol), sodium bicarbonate (5.03 g, 60 mmol) and water (100 mL). The resulting mixture is stirred rapidly for 20 minutes while warming from 5 °C to ambient temperature. The mixture is extracted with dichloromethane (3 x 75 mL), then the combined organic extracts are dried (MgSO_4), filtered, and concentrated under reduced pressure. The

resulting residue is purified *via* preparative chromatography (silica gel; water saturated ethyl acetate) to afford the desired (3'-keto)cyclosporin A.

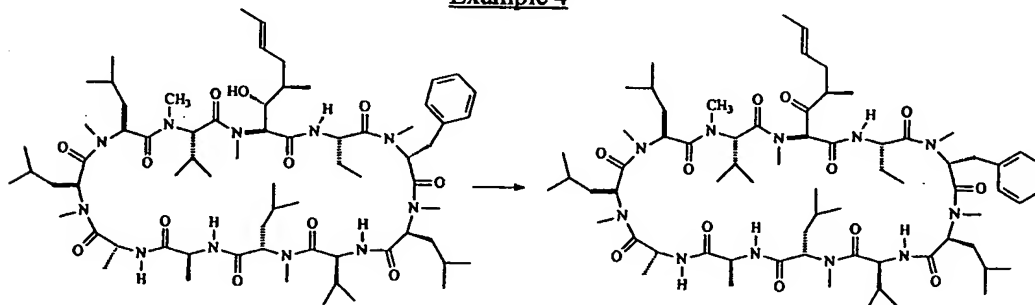
Example 2



(N⁵-1-propenyl) Cyclosporin A: Cyclosporin A (2 g, 1.66 mmol; commercially available from Alexis Corporation, San Diego, CA) is dissolved in tetrahydrofuran (40 mL) at ambient temperature under inert atmosphere. The reaction solution is cooled to -78 °C and 1N phosphazene base P4-*t*-butyl solution (8.4 mL, 8.32 mmol; commercially available from Fluka Chemika AG, Buchs, Switzerland) is added dropwise over 5 minutes. The solution is stirred an additional 5 minutes at -78 °C followed by the dropwise addition of allyl bromide (1.16 mL, 13.3 mmol) over 1 minute. The solution is stirred for 90 minutes at -78 °C followed by the addition of 1N aqueous citric acid (20 mL). The mixture is poured into a solution of 1N aqueous citric acid (80 mL) and brine (20 mL), then extracted with ethyl acetate (3 x 50mL). The combined organic extracts are dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue is purified *via* preparative chromatography (silica gel; gradient elution with 1:1 to 1:0 (ethyl acetate : dichloromethane)) to afford the desired (N⁵-allyl)cyclosporin A.

Example 3

(N-Me-D-Phe)³-CsA: Cyclosporin A (5.0 g, 4.16 mmol; commercially available from Alexis Corporation, San Diego, CA) is dissolved in tetrahydrofuran (250 mL) at ambient temperature under inert atmosphere. The reaction is cooled to -78 °C and 1N lithium bis(trimethylsilyl)amide in tetrahydrofuran (41.6 mL, 41.6 mmol; commercially available from Aldrich Chemical Co., Milwaukee, WI) is added dropwise over 5 minutes. After stirring at -78 °C for about 1.5 hours, benzyl bromide (14.2 g, 83.2 mmol; commercially available from Aldrich Chemical Co., Milwaukee, WI) is added dropwise over 5 minutes. The reaction mixture is stirred at -78 °C for about 1 hour, then at 0 °C for about 1.5 hours, and finally at ambient temperature for about 45 minutes. Water (50 mL) is added and the reaction mixture is concentrated under reduced pressure to remove the tetrahydrofuran. The mixture is then poured onto water (150 mL) and extracted with diethyl ether (3 x 200 mL). The combined ether extracts are washed with 1:1 water : brine (100 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude product is purified *via* preparative chromatography (silica gel; gradient elution 99:1 to 96:4 dichloromethane : methanol) to afford the desired (N-Me-D-Phe)³-CsA.

Example 4

(3'-Keto)¹(N-Me-D-Phe)³-CsA: Dess-Martin periodinane (6.50 g, 15.33 mmol; prepared according to the procedure reported in Ireland et al., "An Improved Procedure for the Preparation of the Dess-Martin Periodinane", *Journal of Organic Chemistry*, Vol. 58, p. 2899 (1993)) is combined with dichloromethane (20 mL) and stirred for 10 minutes at ambient temperature. The solution is chilled to 0 °C followed by the dropwise addition of (N-Me-D-Phe)³-CsA (2.20 g, 1.70 mmol; prepared according to Example 3 herein) in dichloromethane (40 mL) over 10 minutes. After the mixture is stirred at 0 °C for about 2.5 hours, additional Dess-Martin periodinane (2.16 g, 5.1 mmol) is added to the reaction. The reaction mixture is stirred for an additional 5 hours at 0 °C. A solution of sodium thiosulfate (17 g, 107.3 mmol), sodium bicarbonate (15.45 g, 183.9 mmol), and water (300 mL) is added. The resulting mixture is stirred rapidly for about 20 minutes at ambient temperature. The mixture is extracted with dichloromethane (3 x 100 mL), then the combined organic extracts are dried (MgSO₄), filtered, and concentrated under reduced pressure. The resulting residue is purified *via* preparative chromatography (silica gel; gradient elution 99:1 to 96:4 dichloromethane : methanol) to afford the desired (3'-Keto)¹(N-Me-D-Phe)³-CsA.

Use of the Present Compounds

The methods of the present invention are performed by administration of a compound having a structure as described herein and, preferably, a pharmaceutically-acceptable or cosmetically-acceptable carrier.

The compounds herein may be used for the treatment of such conditions as treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth. Such conditions may manifest themselves in, for example, alopecia, including male pattern baldness and female pattern baldness.

The compounds of the present invention are, as defined herein, non-immunosuppressive.

Preferably, in the methods of the present invention, the compounds are formulated into pharmaceutical or cosmetic compositions for use in treatment or prophylaxis of conditions such as the foregoing. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. (1990).

Typically, from about 5 mg to about 3000 mg, more preferably from about 5 mg to about 1000 mg, more preferably from about 10 mg to about 100 mg, of a compound having a structure as described herein is administered per day for systemic administration. It is

understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on various factors. The specific dosage of the compound to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific compound used, the treatment indication, the efficacy of the compound, the personal attributes of the subject (such as, for example, weight, age, sex, and medical condition of the subject), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

According to the present invention, the subject compounds are co-administered with a pharmaceutically-acceptable or cosmetically-acceptable carrier (herein collectively described as "carrier"). The term "carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with a compound of the present invention, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. Carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal, preferably mammal (most preferably human), being treated. The carrier can itself be inert or it can possess pharmaceutical and / or cosmetic benefits of its own.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical, nasal, ocular or parenteral administration. Of these, topical and / or oral administration are especially preferred with topical being most preferred. Depending upon the particular route of administration desired, a variety of carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active or cosmetically-active materials may be included which do not substantially interfere with the activity of the compound of the present invention. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

Some examples of substances which can serve as carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch;

cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a carrier to be used in conjunction with the subject compound is typically determined by the way the compound is to be administered.

In particular, carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of a compound used in the present invention. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The carriers suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically

comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Orally administered compositions also include liquid solutions, emulsions, suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compounds of the present invention may also be topically administered. The carrier of the topical composition preferably aids penetration of the present compounds into the skin to reach the environment of the hair follicle. Topical compositions of the present invention may be in any form including, for example, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like.

Topical compositions containing the active compound can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloë vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, *iso*-propyl isostearate, stearic acid, *iso*-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-*n*-butyl sebacate, *iso*-propyl myristate, *iso*-propyl palmitate, *iso*-propyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, *iso*-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, *iso*-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

The compounds used in the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. A preferred formulation for topical delivery of the present compounds utilizes liposomes such as described in Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An *in vitro* Study Using Hairless Mouse Skin", S.T.P. Pharma Sciences, Vol. 3, pp. 404 - 407 (1993); Wallach and Philippot, "New Type of Lipid Vesicle: Novasome[®]", Liposome Technology, Vol. 1, pp. 141 - 156 (1993); Wallach, U.S. Patent No. 4,911,928, assigned to Micro-Pak, Inc., issued March 27, 1990; and Weiner et al., U.S. Patent No. 5,834,014, assigned to The University of Michigan and Micro-Pak, Inc., issued November 10, 1998 (with respect to Weiner et al., with a compound as described herein administered in lieu of, or in addition to, minoxidil).

The compounds of the present invention may also be administered by iontophoresis. See, e.g., internet site www.unipr.it/arpa/dipfarm/erasmus/erasm14.html; Banga et al., "Hydrogel-

based Iontotherapeutic Delivery Devices for Transdermal Delivery of Peptide/Protein Drugs", *Pharm. Res.*, Vol. 10 (5), pp. 697-702 (1993); Ferry, "Theoretical Model of Iontophoresis Utilized in Transdermal Drug Delivery", *Pharmaceutical Acta Helvetiae*, Vol 70, pp. 279-287 (1995); Gangarosa et al., "Modern Iontophoresis for Local Drug Delivery", *Int. J. Pharm.*, Vol. 123, pp. 159-171 (1995); Green et al., "Iontophoretic Delivery of a Series of Tripeptides Across the Skin *in vitro*", *Pharm. Res.*, Vol 8, pp. 1121-1127 (1991); Jadoul et al., "Quantification and Localization of Fentanyl and TRH Delivered by Iontophoresis in the Skin", *Int. J. Pharm.*, Vol. 120, pp. 221-8 (1995); O'Brien et al., "An Updated Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy", *Drugs*, Vol. 37, pp. 233-309 (1989); Parry et al., "Acyclovir Bioavailability in Human Skin", *J. Invest. Dermatol.*, Vol. 98 (6), pp. 856-63 (1992); Santi et al., "Drug Reservoir Composition and Transport of Salmon Calcitonin in Transdermal Iontophoresis", *Pharm. Res.*, Vol 14 (1), pp. 63-66 (1997); Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: I. pH and Ionic Strength", *J. Control. Release*, Vol. 38, pp. 159-165 (1996); Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: II. Electrode Chamber Formulation", *J. Control. Release*, Vol. 42, pp. 29-36 (1996); Rao et al., "Reverse Iontophoresis: Noninvasive Glucose Monitoring *in vivo* in Humans", *Pharm. Res.*, Vol. 12 (12), pp. 1869-1873 (1995); Thysman et al., "Human Calcitonin Delivery in Rats by Iontophoresis", *J. Pharm. Pharmacol.*, Vol. 46, pp. 725-730 (1994); and Volpato et al., "Iontophoresis Enhances the Transport of Acyclovir through Nude Mouse Skin by Electropulsion and Electroosmosis", *Pharm. Res.*, Vol. 12 (11), pp. 1623-1627 (1995).

The compositions of the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules which can function in different ways to enhance hair growth effects of a compound of the present invention. Particular classes of activity enhancers include other hair growth stimulants and penetration enhancers.

Additional hair growth stimulants can be chosen from a wide variety of molecules which can function in different ways to enhance the hair growth effects of a compound of the present invention. These optional other hair growth stimulants, when present, are typically employed in the compositions herein at a level ranging from about 0.01% to about 15%, preferably from about 0.1% to about 10%, most preferably from about 0.5% to about 5% by weight of the composition.

Vasodilators such as potassium channel agonists including, for example, minoxidil and minoxidil derivatives such as aminexil and such as those described in U.S. Patent 3,382,247, U.S. Patent 5,756,092, issued May 26, 1998, U.S. Patent 5,772,990, issued June 30, 1998, U.S. Patent 5,760,043, issued June 2, 1998, U.S. Patent 3,289,14, issued July 12, 1994, U.S. Patent

5,466,694, issued November 14, 1995, 5,438,058, issued August 1, 1995, and U.S. Patent 4,973,474, issued November 27, 1990, (all of which are herein incorporated by reference), and cromakalin and diazoxide can be used as an additional hair growth stimulant in the compositions herein.

One suitable class of additional hair growth stimulant for use herein are antiandrogens. Examples of suitable antiandrogens may include, but are not limited 5- α -reductase inhibitors such as finasteride and those described in U.S. Patent 5,516,779, issued May 14, 1996 (herein incorporated by reference) and in Nane et al., Cancer Research 58, "Effects of Some Novel Inhibitors of C17,20-Lyase and 5 α -Reductase *in vitro* and *in vivo* and Their Potential Role in the Treatment of Prostate Cancer," as well as cyproterone acetate, azelaic acid and its derivatives and those compounds described in U.S. Patent 5,480,913, issued January 2, 1996, flutamide, and those described in U.S. Patents 5,411,981, issued May 2, 1995, U.S. Patent 5,565,467, issued October 15, 1996 and U.S. Patent 4,910,226, issued March 20, 1990, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are FK506 analogs such as those described in McIver et al., U.S. Patent Application Serial No. 09/400,681, filed September 21, 1999; McIver et al., U.S. Patent Application Serial No. 09/400,682, filed September 21, 1999; McIver et al., U.S. Patent Application Serial No. 09/400,679, filed September 21, 1999; Tiesman et al., U.S. Patent Application Serial No. 09/400,021, filed September 21, 1999; Fulmer et al., U.S. Patent Application Serial No. 09/400,425, filed September 21, 1999; U.S. Provisional Patent Application No. 60/147,279, Degenhardt et al., filed August 5, 1999; U.S. Provisional Patent Application No. 60/147,313, Degenhardt et al., filed August 5, 1999; U.S. Provisional Patent Application No. 60/147,280, Degenhardt et al., filed August 5, 1999; U.S. Provisional Patent Application No. 60/147,278, Degenhardt et al., filed August 5, 1999; and U.S. Provisional Patent Application No. 60/147,276, Eickhoff et al., filed August 5, 1999; all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are antimicrobials such as selenium sulfide, ketoconazole, triclocarbon, triclosan, zinc pyrithione, itraconazole, asiatic acid, hinokitiol, mipirocin and those described in EPA 0,680,745 (herein incorporated by reference), clinacycin hydrochloride, benzoyl peroxide, benzyl peroxide and minocyclin.

Anti-inflammatories can also be incorporated into the compositions herein as an optional hair growth stimulant. Examples of suitable anti-inflammatories may include glucocorticoids such as hydrocortisone, mometasone furoate and prednisolone, nonsteroidal anti-inflammatories including cyclooxygenase or lipoxygenase inhibitors such as those described in U.S. Patent

5,756,092, and benzydamine, salicylic acid, and those compounds described in EPA 0,770,399, published May 2, 1997, WO 94/06434, published March 31, 1994, and FR 2,268,523, published November 21, 1975, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are thyroid hormones and derivatives and analogs thereof. Examples of suitable thyroid hormones for use herein may include triiodothyronine. Examples of thyroid hormone analogs which may be suitable for use herein include those described in U.S. Provisional Patent Application No. 60/136,996, Zhang et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,024, Zhang et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,022, Zhang et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,023, Zhang et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,052, Youngquist et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,063, Youngquist et al., filed June 1, 1999, and U.S. Provisional Patent Application No. 60/136,958, Youngquist et al., filed June 1, 1999.

Prostaglandin agonists or antagonists can also be used as optional hair growth stimulants in the compositions herein. Examples of suitable prostaglandins agonists or antagonists include latanoprost and those described in WO 98/33497, Johnstone, published August 6, 1998, WO 95/11003, Stjerschantz, published April 27, 1995, JP 97-100091, Ueno and JP 96-134242, Nakamura.

Another class of optional hair growth stimulants for use herein are retinoids. Suitable retinoids may include isotretinoin, acitretin, and tazarotene.

Another class of optional hair growth stimulants for use herein are triterpenes such as, for example, those disclosed in Bradbury et al., U.S. Patent Application Serial No. 09/353,408, "Method for Regulating Hair Growth", filed July 15, 1999 and Bradbury et al., U.S. Patent Application Serial No. 09/353,409, "Compositions Which Contain Triterpenes for Regulating Hair Growth", filed July 15, 1999, each incorporated by reference in their entirety.

Other classes of optional hair growth stimulants for use herein include flavinoids, ascomycin derivatives and analogs, histamine antagonists such as diphenhydramine hydrochloride, other triterpenes such as oleanolic acid and ursolic acid and those described in U.S. Patent 5,529,769, JP 10017431, WO 95/35103, U.S. Patent 5,468,888, JP 09067253, WO 92/09262, JP 62093215, U.S. Patent 5,631,282, U.S. Patent 5,679,705, JP 08193094, saponins such as those described in EP 0,558,509 to Bonte et al., published September 8, 1993 and WO 97/01346 to Bonte et al., published January 16, 1997 (both of which are herein incorporated by reference in their entirety), proteoglycanase or glycosaminoglycanase inhibitors such as those described in U.S. Patents 5,015,470, issued May 14, 1991, U.S. Patent 5,300,284, issued April 5,

1994 and U.S. Patent 5,185,325, issued February 9, 1993 (all of which are herein incorporated in their entirety by reference) estrogen agonists and antagonists, pseudoterins, cytokine and growth factor promoters, analogs or inhibitors such as interleukin1 inhibitors, interleukin-6 inhibitors, interleukin-10 promoters, and tumor necrosis factor inhibitors, vitamins such as vitamin D analogs and parathyroid hormone antagonists, Vitamin B12 analogs and panthenol, interferon agonists and antagonists, hydroxyacids such as those described in U.S. Patent 5,550,158, benzophenones, and hydantoin anticonvulsants such as phenytoin.

Other additional hair growth stimulants are described in detail in, for example, JP 09-157,139 to Tsuji et al., published June 17, 1997; EP 0277455 A1 to Mirabeau, published August 10, 1988; WO 97/05887 to Cabo Soler et al., published February 20, 1997; WO 92/16186 to Bonte et al., published March 13, 1992; JP 62-93215 to Okazaki et al., published April 28, 1987; U.S. Patent 4,987,150 to Kurono et al., issued January 22, 1991; JP 290811 to Ohba et al., published October 15, 1992; JP 05-286,835 to Tanaka et al., published November 2, 1993, FR 2,723,313 to Greff, published August 2, 1994, U. S. Patent 5,015,470 to Gibson, issued May 14, 1991, U.S. Patent 5,559,092, issued September 24, 1996, U.S. Patent 5,536,751, issued July 16, 1996, U.S. Patent 5,714,515, issued February 3, 1998, EPA 0,319,991, published June 14, 1989, EPA 0,357,630, published October 6, 1988, EPA 0,573,253, published December 8, 1993, JP 61-260010, published November 18, 1986, U.S. Patent 5,772,990, issued June 30, 1998, U.S. Patent 5,053, 410, issued October 1, 1991, and U.S. Patent 4,761,401, issued August 2, 1988, all of which are herein incorporated by reference.

Non-limiting examples of penetration enhancers which may be used in the compositions herein include, for example, 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, POE(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, POE(2) methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, POE ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, *iso*-propyl palmitate, ethyl laurate, 2-ethyl-hexyl pelargonate, *iso*-propyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hydroxypropanoic acid, 2-hydroxyoctanoic acid, dimethyl sulphoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-

pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-*m*-toluamide, and, 1-dodecylazacycloheptan-2-one.

In all of the foregoing, of course, the compounds of the invention can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication.

Examples of Composition Administration

The following examples do not limit the invention, but provide guidance to the skilled artisan to perform the methods of the present invention. In each example, a compound other than the one mentioned may be substituted by another having a structure as described herein.

Example A

A composition for topical administration is made, comprising:

<u>Component</u>	<u>Amount</u>
Compound of Example 2	5 %
Ethanol	57 %
Propylene Glycol	19 %
Dimethyl Isosorbide	19 %

A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 6 weeks, the above composition is daily administered topically to the subject.

Example B

A composition for topical administration is made according to the method of Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An *in vitro* Study Using Hairless Mouse Skin", S.T.P. Pharma Sciences, Vol. 3, pp. 404 - 407 (1993), using the compound of Example 1 in lieu of cyclosporin A and using the Novasome 1 for the non-ionic liposomal formulation.

A human male subject suffering from male pattern baldness is treated each day with the above composition. Specifically, for 6 weeks, the above composition is administered topically to the subject.

Example C

Four different shampoo compositions are made as follows:

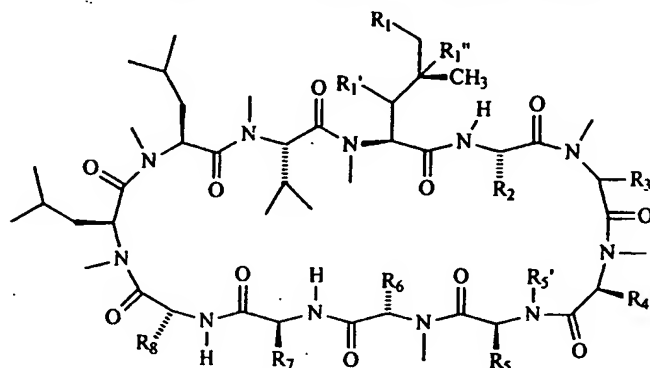
	Ex. C-1	Ex. C-2	Ex. C-3	Ex. C-4
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Component				
Ammonium Lauryl Sulfate	11.5 %	11.5 %	9.5 %	7.5 %
Ammonium Laureth Sulfate	4 %	3 %	2 %	2 %
Cocamide MEA	2 %	2 %	2 %	2 %
Ethylene Glycol Distearate	2 %	2 %	2 %	2 %
Cetyl Alcohol	2 %	2 %	2 %	2 %
Stearyl Alcohol	1.2 %	1.2 %	1.2 %	1.2 %
Glycerin	1 %	1 %	1 %	1 %
Polyquaternium 10	0.5 %	0.25 %	-	-
Polyquaternium 24	-	-	0.5 %	0.25 %
Sodium Chloride	0.1 %	0.1 %	0.1 %	0.1 %
Sucrose Polyesters of Cottonate Fatty Acid	3 %	3 %	-	-
Sucrose Polyesters of Behenate Fatty Acid	2 %	3 %	-	-
Polydimethyl Siloxane	-	-	3 %	2 %
Cocaminopropyl Betaine	-	1 %	3 %	3 %
Lauryl Dimethyl Amine Oxide	1.5 %	1.5 %	1.5 %	1.5 %
Decyl Polyglucose	-	-	1 %	1 %
DMDM Hydantoin	0.15 %	0.15 %	0.15 %	0.15 %
Compound of Example 1	5 %	-	-	-
Compound of Example 2	-	2 %	-	-
Compound of Example 3	-	-	3 %	-
Compound of Example 4	-	-	-	6 %
Minoxidil	-	-	-	2 %
Phenoxyethanol	0.5 %	0.5 %	0.5 %	0.5 %
Fragrance	0.5 %	0.5 %	0.5 %	0.5 %
Water	q.s.	q.s.	q.s.	q.s.

A human subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 12 weeks, the above shampoo is used daily by the subject.

What is claimed is:

1. A method of treating hair loss characterized by administering to a mammal a composition characterized by a non-immunosuppressive compound having the structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein:

- (a) R_1 is selected from the group consisting of 1-propenyl, propyl, 3-hydroxy-1-propenyl, -O-methyl, -O-*p*-benzoyl benzyl, and hydroxy;
- (b) R_1' is selected from the group consisting of hydroxy, oxo, and acyloxy;
- (c) R_1'' is selected from the group consisting of hydrogen and methyl;
- (d) R_2 is selected from the group consisting of ethyl, *n*-butyl, 2-hydroxypropyl, 2-methoxypropyl, 1-methylpropyl, and 2-acyloxy-propyl;
- (e) R_3 is selected from the group consisting of hydrogen, methyl, benzyl, 1-propenyl, and 2-methyl-3-hydroxy-propyl;
- (f) R_4 is substituted or unsubstituted $C_1 - C_6$ straight or branched alkyl;
- (g) R_5 is substituted or unsubstituted $C_1 - C_6$ straight or branched alkyl;
- (h) R_5' is selected from the group consisting of hydrogen, methyl, benzyl, *p*-fluorobenzyl, 1-propenyl, and 1-phenyl-1-propenyl;
- (i) R_6 is selected from the group consisting of 2-methylpropyl, 2-methyl-3-hydroxypropyl, methyl, and ethyl;
- (j) R_7 is selected from the group consisting of methyl and phenyl; and
- (k) R_8 is selected from the group consisting of methyl and hydroxymethyl.

2. A method according to Claim 1 wherein:

- (a) R_1' is selected from the group consisting of hydroxy and oxo;
 - (b) R_1'' is hydrogen;
 - (c) R_2 is selected from the group consisting of ethyl, *n*-butyl, 2-hydroxypropyl, and 2-methoxypropyl; and
 - (d) R_3 is selected from the group consisting of hydrogen, methyl, and benzyl.
3. A method according to any of the preceding claims wherein:
- (a) R_4 is selected from the group consisting of 2-methylpropyl, 2-methyl-3-hydroxypropyl, 2-methylbutyl, *iso*-propyl, 2-hydroxypropyl, and methyl;
 - (b) R_5 is selected from the group consisting of 2-methylpropyl, *n*-butyl, and *iso*-propyl; and
 - (c) R_5' is selected from the group consisting of hydrogen, methyl, and 1-propenyl.
4. A method according to any of the preceding claims wherein R_2 is ethyl and R_3 is selected from the group consisting of hydrogen and benzyl.
5. A method according to any of the preceding claims wherein R_5' is selected from the group consisting of hydrogen and 1-propenyl and R_4 is 2-methylpropyl.
6. A method according to any of the preceding claims wherein R_5 is *iso*-propyl and R_6 is 2-methylpropyl.
7. A method according to any of the preceding claims wherein R_7 is methyl and R_8 is methyl.
8. A method according to Claim 11 wherein R_1 is 1-propenyl and R_1' is oxo.
9. A method according to any of the preceding claims wherein the administration is topical.
10. A composition useful for treating hair loss comprising a non-immunosuppressive compound according to any of the preceding claims and a second compound selected from the group consisting of minoxidil and finasteride.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/05300

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 807 820 A (P.M. ELIAS) 15 September 1998 (1998-09-15) cited in the application claim 1 column 2, line 53-57	1

☐ Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 August 2000

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INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 00/05300

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5807820 A	15-09-1998	BE 1002266 A	13-11-1990
		CH 679119 A	31-12-1991
		DE 3915617 A	16-11-1989
		FR 2631235 A	17-11-1989
		GB 2218334 A,B	15-11-1989
		IT 1232832 B	05-03-1992
		JP 1977742 C	17-10-1995
		JP 2017127 A	22-01-1990
		JP 7005473 B	25-01-1995